REMARKS/ARGUMENTS

STATUS OF THE CLAIMS.

Claims 1, 3-5, 7-26, 28-133, and 135-138 are currently pending in the application, claims 2, 6, 27, 134, and 139 were previously cancelled and claims 50, 51, 53, 55-63, 116 and 119-132 were previously withdrawn from current consideration. Applicants note with thanks, Examiner Whaley's clarification that claim 117 is not withdrawn. Claims 1, 11, 18, 19, 20, 108, 133, and 138 are amended herein to more clearly describe currently claimed embodiments of the invention while claim 17 is cancelled and claims 140 and 141 are newly added. These changes introduce no new matter and support is present in the application and claims as originally filed. The changes are made without prejudice and are not to be construed as abandonment of any previously claimed subject matter or agreement with any objection or rejection of record. Accordingly, entry of the Amendment is respectfully requested.

AMENDMENTS TO THE CLAIMS

Claims 1, 11, 18, 19, 20, 108, 133, and 138 are amended herein, and claims 140 and 141 are newly added, to more clearly present the currently claimed embodiments. Support for the changes is replete throughout the specification, claims and figures as originally filed. Thus, for example, changes to claim 1 concerning collecting and pooling of case and control samples can be found in the original wording of claim 1, in prior claim 17 (whose limitations are incorporated into amended claim 1 and which is cancelled herein), paragraph 66, etc. Changes to claim 1 concerning determination of relative allele frequency with probe sets are supported by, e.g., claim 28, and paragraphs 109-116, 125-130, 131-138, etc. Additional changes to claim 1 arise from reorganization of the language present within the unamended claim.

Claim 11 is amended to correct a grammatical error.

Changes to claims 18-20 are merely to amend their dependency. Since the prior limitations of claim 17 are now incorporated into claim 1, claims 18-20 are amended to depend from claim 1.

Claim 108 is amended to add in language concerning assays of determinable markers. Support for such change can be found in, e.g., paragraphs 67-73 and 76-83 of the specification.

Claims 133 and 138 are amended herein to more closely match the other amended independent claims. Support for the changes to claims 133 and 138 can be found in paragraphs 9 and 11-12, and in the locations cited above for the changes to claim 1.

Claims 140 and 141 are newly added herein. Support for such claims can be found in, e.g., paragraphs 111-112 of the specification.

Because the amendments herein add no new matter to the claims, their entry is respectfully requested. Of course, it will be appreciated that recitation of specific support is not meant to be limiting. In other words, further support for the changes can be found in additional locations within the specification.

REJECTIONS TO THE CLAIMS

35 U.S.C. §101

Claims 108-115, and 117 are currently rejected under 35 U.S.C. §101 as allegedly drawn to non-statutory subject matter. Applicants herein amend, and respectfully traverse any rejection remaining after entry of the current amendment.

While Applicants believe the unamended claims to be drawn to allowable statutory subject matter under 35 U.S.C. §101, in order to further prosecution, and as helpfully suggested by the Examiner, Applicants herein amend claim 108 (and hence its dependents) to explicitly state that the determination of the signal intensities from the reference and alternate nucleic acid segments in their respective pools is done by one or more assays of a determinable marker. Support for such change is found in, e.g., paragraphs 67-73 and 76-83.

Because the amended language of the claim explicitly recites a step comprising physical transformation of matter (i.e., assays), the claim is not drawn to non-statutory subject matter under 35 U.S.C. §101 and Applicants respectfully request that the rejection be withdrawn.

35 U.S.C. §112 Second Paragraph

Indefiniteness

Claims 1, 3, 4, 5, 7-26, 28-49, 52, 54, and 64-107 are rejected in the current Office Action under 35 U.S.C. §112, second paragraph, as allegedly indefinite by failing to particularly

point out and distinctly claim the subject matter regarded by Applicants as the invention. The Office Action alleges that claim 1, and hence its dependents, is indefinite in use of "segments collected from a case group and a control group," "a first sample collected from the control group," and "a second sample collected from the control group," since it is allegedly unclear whether such segments/samples collected from the case and control groups are intended to be further limitations of the nucleic acid segments or active methods steps (e.g., collecting). Applicants herein amend and traverse any rejection remaining after the current amendment.

In order to more clearly present the current embodiment, and as helpfully suggested by the Examiner, Applicants herein amend claim 1, and hence its dependents, to recite active collecting steps. Support for such change is replete throughout the application as filed. For example, support can be found in prior claim 17, whose limitations are now incorporated into claim 1 and which is cancelled herein, as well as in numerous paragraphs in the specification that describe the actions of collecting samples for case and control group members (e.g., paragraph 66 which states that "biological samples...are taken from individuals").

The determination of indefiniteness is whether "those skilled in the art would understand the scope of the claim when the claim is read in the light of the specification." *Breuer Electric Mfg. Co. v. Tennant Co.*, 44 USPQ2d 1259, 1266 (Ill. 1997). Applicants believe that those of skill in the art would grasp the scope of the active step of collecting involved in the current claims, i.e., the claims require actual collecting of samples from members of the case and control groups.

Thus, Applicants believe that the description of "collecting" in claim 1 and its dependents is clear and not indefinite and that those skilled in the art will easily understand the scope of the amended claim. Because the claim is not indefinite, Applicants respectfully request that the rejection be withdrawn.

U.S.C. §102(b)

Schork

Claims 1, 4, 5, 7, 11-22, and 133 are rejected in the current Office Action under 35 U.S.C. §102(b) as allegedly anticipated by Schork, *et al.*, USPN 6,291,182. Applicants respectfully traverse.

The Office Action alleges that Schork teaches "methods, software, and apparati for determining whether a genomic region harbors a gene with a detectable trait" and cites specific passages within Schork as purportedly teaching specific limitations of claims 1, 4, 5, 7, 11-22, and 133 of the current application.

In order for a reference to anticipate a claim "the reference must teach every element of the claim." M.P.E.P. §2131. Additionally, "every element of the claimed invention must be identically shown in a single reference," and the "elements must be arranged as in the claim under review." *See In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

While Applicants believe the unamended claims to be free of Schork as written, in order to more plainly claim the current embodiment, Applicants herein amend claim 1 (from which claims 4, 5, 7, and 11-22 depend) and claim 133. The claims are amended, *inter alia*, to specifically read a first and a second pooled sample collected from a case or control group. Again, Applicants believe that unamended claims 1 and 133 already encompass this limitation. For example, a sample collected from a group, as is required in claims 1 and 133, implicitly requires pooling in order to create a single sample from numerous group members. However, in addition to the language present in the unamended claims, support for the changes can be found in the application at, e.g., paragraphs 67-73, 79-83, prior claim 17, etc. Because such changes to claims 1 and 133 add no new matter, and, indeed, are merely clarifications of limitations already present within the claims, Applicants respectfully request that the changes be entered.

Comparison of the teachings of Schork and the currently claimed embodiments shows that Schork does not present all elements of the current claims. For example, Schork does not teach "determining ... relative allele frequency at the interrogation position in...[a] pooled sample," e.g., as is collected by "pooling biological samples from individuals" in a case or control group, because Schork does not describe or even suggest pooling of biological samples from case or control groups

to produce pooled samples to be used for characterizing an interrogation position in nucleic acid segments.

The Office Action states that Schork teaches "[p]ooling of genomic DNA samples, characterization of polymorphisms using sequence evaluation using software designed for detecting presence of biallelic sites...among pooled fragments" in column 46 in Example 6. However, while Schork describes "pooling" of samples prior to sequencing as a means to identify polymorphisms, the samples pooled in Schork are not from a case or control group and so are not analogous to the pooled samples of the presently claimed invention. As explained in Schork in examples 5 and 6 and in the section entitled "Identification of biallelic markers" starting on column 10, line 45, the pooled nucleic acid samples are not collected from a case or control group. Rather, fragments from unrelated individuals are grouped together without any suggestion of grouping them according to a phenotypic trait of interest, as taught by the instant invention. Thus, the "pooled" samples in Schork do not comprise pooled case or pooled control samples.

In addition, further examination of Schork clearly shows that even the use of the pooled DNA in Example 6 is not the same as the use of the pooled case and control samples present in the current claims since the pooled DNA of Example 6 in Schork was used to detect the presence of biallelic sites in the fragments, not to characterize the interrogation position (e.g., determine relative allelic frequency of an interrogation position in case and control groups) as is done in the current claims. This difference in usage is related to the difference in composition of the samples (i.e., Schork and those of the present invention). Schorks' are compared "in order to generate polymorphisms having the adequate informative content to be used biallelic markers for genetic mapping." Thus, the "pooled" sample in Schork is used to find biallelic sites in a population, not to characterize them as is done in the current methods through characterization of an interrogation position in both case and control groups.

Thus, because Schork does not present all elements of the current claims, it cannot anticipate the current claims and Applicants respectfully request that the rejection be withdrawn.

U.S.C. §103(a)

Fan, Webster, and Kellam

Claims 1, 3-5, 7, 10, 11, 15, 17-21, 29-31, 33-36, 40, 41-43, 47, 48-52, 75, 108, 109, 111-114, 133, and 135-138 are rejected in the current Office Action as allegedly obvious in regard to Fan, *et al.*, *Genome Research*, 2000, 10:853-860 in light of Webster, *et al.*, US Pub. No. 2002/0183933, and Kellam, *et al.*, *Antimicrobial Agents and Chemotherapy*, 1994, 38(1):23-30. Applicants herein amend and respectfully traverse any rejection remaining after entry of the amendment.

Analysis under the recently reaffirmed *Graham v John Deere* standard confirms that the present claims are not obviousness in light of the cited references. As recently reaffirmed by the Supreme Court in *KSR International Co. v. Teleflex* (550 U.S. ____ (2007), the appropriate standard for analyzing questions of obviousness entails that

> "the scope and content of the prior art are determined, differences between the prior art and the claims at issue are analyzed and the level of ordinary skill in the pertinent art is resolved. Against this background the obviousness or non-obviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unresolved needs, failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter to be patented.
>
> *Id.* quoting *Graham v. John Deere of Kansas City* 383 U.S. 1, 17-18.

The Graham factors, in turn, have long been interpreted by the Patent Office, e.g., M.P.E.P §§ 2142 and 2143, as including determination of whether the prior art meets three basic requirements. First, the prior art reference must teach all of the limitations of the claims. M.P.E.P § 2143.03. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. M.P.E.P. § 2143.01. Third, there must be a reasonable expectation of success in combining the teachings. M.P.E.P. § 2143.02. The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure. M.P.E.P. § 2143.

By applying the *KSR/Graham* standard to the present rejection, the "scope and content" of the prior art can be seen, at most, to relate to devices/methods using high density

oligonucleotide Tag arrays to determine allelic frequency within a single group of nucleic acid segments that is not chosen based on phenotypic trait, i.e., not case/control groups (Fan), use of a computer to analyze nucleic acid hybridization of probes at positions (Webster), and a phenotypic assay for drug susceptibility of HIV isolates to reverse transcriptase inhibitors (Kellam).

Thus, there is a major "difference between the prior art and the claims at issue" since amended claims 1, 133, and 138 (and their dependents) comprise: a computer implemented method characterizing an interrogation position by determining and inputting measure of relative allele frequency at the interrogation position from a pooled case group and a pooled control group wherein measurement of the relative allele frequencies is derived from measurement of intensity signals from probe sets (claim 1), an apparatus having computer code for characterizing an interrogation position by determining relative allele frequency at an interrogation position from a pooled case group and a pooled control group wherein measurement of the relative allele frequencies is derived from measurement of intensity signals from probe sets (claim 133), and a computer program to characterize an interrogation position through determination of relative allele frequency at the interrogation position from a pooled case group and a pooled control group wherein measurement of the relative allele frequencies is derived from measurement of intensity signals from probe sets (claim 138). As can be seen, all of the instant claims comprise use of pooled case and control samples and determination of relative allele frequencies in the pooled samples derived from intensity signals from probe sets, all of which are absent from the cited references (Fan, Webster, or Kellam). Therefore, the references alone or in combination cannot present a *prima facie* case of obviousness since they do not teach or suggest every element of the claimed embodiments as further explained below.

Support for the changes in claims 1, 133, and 138 can be found throughout the specification and claims as originally filed (e.g., claim 28). For example paragraphs 109 *et seq.*, and 125 *et seq.* detail the determination of relative allele frequency through use of intensity signals from probe sets complementary to the nucleic acid segments comprising the interrogation position. Because the changes to the claims present no new matter, Applicants respectfully request that the amendment be entered.

Fan, at most, presents methods of genotyping SNPs through oligonucleotide Tag arrays. Nowhere does Fan teach computer-implemented characterization of an interrogation position

by determining relative allele frequency at that position in case and control groups wherein measurement of the relative allele frequencies is derived from measurement of intensity signals from probe sets as used herein. Fan merely describes analysis of a single group of nucleic acid segments from 44 individuals that were not even indicated to be grouped in regard to the presence/lack of a phenotypic characteristic (i.e., they were not case and control groups). Additionally, Fan is specifically drawn to use of Tag arrays which use an indirect hybridization scheme with probes complementary to SPE probes. Thus, there is no direct hybridization of the target to the DNA analyzed. *See*, e.g., Figure 1 and page 853, col. 2. This is in sharp contrast to the probe sets of the instant invention, which "are complementary, according to the base pairing rules, to the reference forward and reverse sequences and alternate forward and reverse sequences that they are respectively intended to interrogate." *See*, e.g., paragraph 111 of the instant specification. Since the "tag probes" of Fan are clearly not analogous to the "probe sets" as taught by the instant specification and claims, and Fan teaches no other type of probe array, this element is therefore lacking in the disclosure of Fan. Therefore, Fan is lacking case/control groups based on presence/lack of a phenotypic characteristic and so it cannot determine relative allele frequency of such different groups in order to characterize the interrogation position as being associated with the phenotypic characteristic. Additionally, Fan is lacking determination of relative allele frequency at an interrogation position wherein measurement of the relative allele frequencies is derived from measurement of intensity signals from probe sets as in the present invention.

To supply the missing elements, the Office Action points to Webster and Kellam. However, neither reference supplies the necessary missing elements. For example, Webster teaches methods of characterizing gene expression in a sample through measuring expression level and comparing it to a baseline in oligonucleotide arrays. Such is not a comparison of relative allele frequency between phenotypically defined case and control groups wherein measurement of the relative allele frequencies is derived from measurement of intensity signals from probe sets.

Even farther afield, Kellam teaches sensitivity assays associated with HIV (a phenotypic characteristic), but teaches nothing of characterizing an interrogation position through determination of relative allele frequency at an interrogation position in case and control groups wherein measurement of the relative allele frequencies is derived from measurement of intensity signals from probe sets.

The Office Action contends that since Fan allegedly teaches characterization of an interrogation site through inputting of measurements of relative allele frequency in pooled case and control samples that Webster and Kellam are relied upon to teach "computer-aided methods for analyzing nucleic acid hybridization intensities of probes sets at specific interrogation positions...and monitoring gene expression" (Webster) and "rapid phenotypic assay for assessment of drug susceptibility of HIV isolates to reverse transcriptase inhibitors" (Kellam). However, as explained above, Fan is actually missing crucial elements of the current claims (e.g., input of measurements of relative allele frequency from pooled case and control samples, etc.) which are not supplied by Webster and Kellam.

Additionally, while Fan speculates on page 856 that its method might possibly be used in wider applications in estimating allele frequencies, such speculation still does not supply the missing claim elements (determining relative allele frequency of an interrogation position in case and control groups, inputting measurement of allele frequency at an interrogation position in case and control groups wherein measurement of the relative allele frequencies is derived from measurement of intensity signals from probe sets, or the equation of claim 108, etc.).

Thus, the combination of Fan, Webster, and Kellam still fails to supply all the elements of the current claims. Therefore, the combination of references cannot render the current claims obvious and Applicants respectfully request that the rejection be withdrawn.

The Office Action also alleges that claim 1 does not "recite active method steps directed to 'determining relative allele frequencies in a case and a control group'." Applicants herein amend claim 1 to specifically recite determination of relative allele frequency in case and control groups. Support for such change is replete throughout the specification as filed, e.g., claim 28, paragraph 109, *et seq.*, and paragraph 125, *et seq.* Therefore, Applicants respectfully request that the amendment be entered.

Claim 108 was also rejected in the Office Action as allegedly obvious in light of Fan, Webster, and Kellam. As stated above, Applicants respectfully traverse. Claim 108 comprises a method of determining relative allele frequency for an interrogation position by determining a

plurality of intensities of signals from reference and alternate nucleic acid segments and using such pluralities of intensities to calculate the equation $< I_{R,1-i} >/(< I_{A,1-j}> + < I_{R,1-i} >)$ or the equation $< I_{A,1-j}>/(< I_{A,1-j}> + < I_{R,1-i} >)$. In such equations $<I_{R,1-i}>$ is the average of the plurality of intensities of signals from the reference nucleic acid segment, while $< I_{A,1-j} >$ is the average of intensities of signals from the alternate nucleic acid segment. Neither Fan, nor Webster, nor Kellam teaches a method of determining relative allele frequencies through use of such equations. While Fan does include an equation on page 859, the components of the equation do not include averages of pluralities of intensities of signals of reference and alternate nucleic acid segments as in claim 108. Therefore, as with claims 1, 133, and 138 (and their dependents), the combination of Fan, Webster, and Kellam does not teach every element of the current claims and thus the current claims are not obvious in light of the combination. Applicants respectfully request that the rejection be withdrawn.

In sum, under the *KSR/Graham* test, Fan, Webster, and Kellam fail to establish a case for obviousness. Importantly, the combination of references does not provide all of the limitations of the current claims. Without the combination of references presenting all elements of the current claims, the rejection does not establish *prima facie* obviousness and must be withdrawn.

U.S.C. §103(a)

Germer, Webster, and Kroll

Claims 1, 3, 4, 5, 48, 52, 75, 77, 79, 80, 81, 83, 84, 86-90, 98, 99, 100, 103, 104, 108, 109, 111, 112, 113, 135, and 136 are rejected in the current Office Action under 35 U.S.C. §103(a) as allegedly obvious in regard to Germer, *et al.*, *Genome Research*, 2000, 10:258-266, in light of Webster, *et al.*, US Pub. No. 2002/0183933, and Kroll, *et al.*, *Nucleic Acids Research*, 2002 30(11):1-6. Applicants herein amend and respectfully traverse any rejection remaining after entry of the amendment.

Again, analysis under the recently reaffirmed *Graham v. John Deere* standard confirms that the present claims are non-obvious in regard to the cited references. Under the *KSR/Graham* standard the scope and content of the prior art is, at most: Germer - determination of SNP allele frequency through use of kinetic PCR in a single sample (but not within case and control samples and most certainly not with use of measurement of probe intensity signals to derive relative

allele frequency); Webster - computer-aided methods to analyze nucleic acid hybridization to show affinity between hybridization probes and sample nucleic acids (but not within case/control samples and not to derive relative allele frequency from measurement of intensity signals); and Kroll - methods to compare measurements of gene expression data such as normalization, mean, trimmed mean, and standard deviation (but not within case/control samples and not to derive relative allele frequencies from measurement of probe intensity signals).

In contrast to the teachings of the cited references, the instant claims specifically require determining relative allele frequency at an interrogation position in a nucleic acid segment derived from pooled samples collected from a case and a control group wherein determination of relative allele frequency at the interrogation position is derived from measurement of intensity signals from probe sets.

Comparing the cited references against the instant claims shows that the combination of the cited references is at least still missing steps concerning measurement of relative allele frequency in case and control group samples based on a phenotypic trait, and determination of relative allele frequency at the interrogation position derived from measurement of intensity signals from probe sets. While the Office Action points to language in Germer concerning case and control populations, such generalized, speculative discussion still fails to present the specific recited elements of the current claims. Germer actually mentions drawbacks of case/control populations in genome wide scans. *See*, e.g., Germer at 258.

In order to provide the missing elements of Germer, the Office Action refers to Webster and Kroll. However, such references still do not provide the needed elements. For example, as explained above, Webster teaches methods (in a computer) for analyzing nucleic acid hybridization in order to show affinity between hybridization probes and sample nucleic acids, but it certainly does not show relative allele frequency in case and control samples, while Kroll only teaches methods to compare normalization measurements of gene expression. Thus, neither Webster nor Kroll supplies necessary elements for claims 1 and 133 concerning measurement of relative allele frequency in case and control group samples based on phenotypic trait, and determination of relative allele frequency at an interrogation position derived from measurement of intensity signals from probe sets.

Thus, under the KSR/Graham test, Germer, Webster, and Kroll fail to establish *prima facie* obviousness since, e.g., they do not teach all of the necessary elements of the current claims. Applicants therefore, respectfully request that the rejection be withdrawn.

Claim 108 also comprises elements that are not found in the combination of Germer, Webster, and Kroll. For example, none of the references teaches a method of determining relative allele frequencies by computing an equation that comprises averages of pluralities of intensities of signals from reference and alternate nucleic acid segments. Thus, the combination of references does not teach all elements of claim 108 and therefore does not render 108 *prima facie* obvious. Applicants respectfully request that the rejection be withdrawn.

U.S.C. §103(a)

Barcellos, Webster, Kroll, and Xiong

Claims 1, 3, 4, 5, 11, 12, 13, 17-19, 22, 23, 26, 28, 52, 64-68, 72, 75-77, 133, and 135-138 are rejected in the current Office Action under 35 U.S.C. §103(a) as allegedly obvious in regard to Barcellos, *et al.*, *Am. J. Hum. Genet.*, 1997, 61:734-747, in view of Webster, *et al.*, US Pub. No. 2002/0183933 and Kroll, *et al.*, *Nucleic Acids Research*, 202, 30(11):1-6, and further in view of Xiong, *et al.*, *Am. J. Hum. Genet.*, 1999, 64:629-640. Applicants herein amend and respectfully traverse any rejection remaining after entry of the current amendment.

Support for changes to claims 1 and 133 are detailed above. Support for changes to claim 138 can similarly be found in, e.g., original claim 28, paragraph 109, *et seq.*, and paragraph 125, *et seq.*

Here too, analysis under 35 U.S.C. §103(a) indicates that the amended claims are not obvious in regard to the cited references. The scope and content of the prior art is: use of microsatellite markers and electrophoresis sizing in high resolution genome screening (Barcellos); computer-aided methods to analyze nucleic acid hybridization to show affinity between hybridization probes and sample nucleic acids (Webster); methods to compare measurements of gene expression data such as normalization, mean, trimmed mean, and standard deviation (Kroll); and comparison of biallelic and microsatellite markers in gene mapping (Xiong).

In this instance as well, there is a great difference between the current claims and the combined references. Namely, in contrast to the cited references, the current claims (e.g., independent claims 1, 133, and 138) require: the determination of relative allele frequency at an interrogation position in a nucleic acid segment derived from pooled samples collected from a case and a control group wherein relative allele frequency is derived from measurement of intensity signals of probe sets, and inputting such into a computer (claim 1); computer code in an apparatus to determine measurement of relative allele frequency at an interrogation position for a nucleic acid segment derived from pooled case and control samples used to characterize the interrogation position wherein relative allele frequency is derived from measurement of intensity signals of probe sets (claim 133); and computer code with instructions for characterizing a biallelic polymorphism interrogation position in a nucleic acid through determining measures of relative allele frequency at the interrogation positions from pooled case and control groups wherein relative allele frequency is derived from measurement of intensity signals of probe sets (claim 138).

Thus, while Barcellos arguably contains language concerning use of microsatellite markers in case/control gene studies, etc., it is still missing steps concerning measurement of relative allele frequency in case and control group samples (based on phenotypic trait, etc.) wherein relative allele frequency is derived from measurement of intensity signals of probe sets. Barcellos does not even remotely utilize probe sets as described in the present invention. Rather, Barcellos uses electrophoresis and kinetic PCR amplification to analyze microsatellite markers.

Here too, the Office Action points to Webster and Kroll to supply the missing elements, but as indicated above, Webster and Kroll do not supply such necessary missing parts. Again, Webster teaches computer methods for analyzing nucleic acid hybridization in order to show affinity between hybridization probes and sample nucleic acids (with no measurement of relative allele frequencies from phenotypically defined case and control groups wherein relative allele frequency is derived from measurement of intensity signals of probe sets) and Kroll teaches methods to compare normalization of measurements of gene expression (with no measurement of relative allele frequencies from phenotypically defined case and control groups wherein relative allele frequency is derived from measurement of intensity signals of probe sets). Thus, neither Webster nor Kroll supplies the necessary elements for the current claims concerning measurement of relative allele frequency in case and control group samples based on a phenotypic trait, etc.

The Office Action also points to Xiong to supply missing elements. However, while Xiong arguably might include comparison of gene mapping with biallelic markers and microsatellite markers, the combination of the references still does not add up to the current claims. Xiong focuses on theoretical statistical comparison between use of biallelic markers and microsatellite markers. It does not teach determination of relative allele frequency at an interrogation position for pooled case and pooled control groups wherein relative allele frequency is derived from measurement of intensity signals of probe sets.

Therefore, the combination of the cited references does not present all elements of the current claims. Applicants respectfully request that the rejection be withdrawn.

U.S.C. §103(a)

Barcellos, Webster, Kroll, Xiong, Mathworld, and County Loan Calculation Proc.

Claims 78-83 are rejected in the current Office Action under 35 U.S.C. §103(a) as allegedly obvious in regard to Barcellos, *et al.*, *Am. J. Hum. Genet.*, 1997, 61:734-747, in view of Webster, *et al.*, US Pub. No. 2002/0183933, Kroll, *et al.*, *Nucleic Acids Research*, 202, 30(11):1-6, and Xiong, *et al.*, *Am. J. Hum. Genet.*, 1999, 64:629-640, in further view of MathWorld (http://mathworld.wolfram.com/Pairedt-Test.html), 1999, CRC Press, LLC, p.1-2, and The 2002 County Loan Rate Calculation Procedure, 2002, p. 1. Applicants herein amend and respectfully traverse to the extent that any rejections remain after entry of the amendment.

As described above, the combination of Barcellos, Webste, Kroll, and Xiong fails to present all elements of the amended independent claims from which claims 78-83 depend. The addition of MathWorld and Count Loan Rate (CLRCP) to the combination still fails to present all elements of such claims, and thus, fails to present *prima facie* obviousness of claims 78-83.

Both MathWorld and CLRCP teach various calculations for determining the paired t-test (MathWorld) and Olympic Averages for data (CLRCP), however, neither reference teaches anything concerning determination of relative allele frequency in a computer system based on phenotypically defined case and control groups wherein determination of relative allele frequency at the interrogation position is derived from measurement of intensity signals of probe sets. As detailed above, the underlying combination of Barcellos, Webster, Kroll, and Xiong fails to supply such

needed elements. Therefore, addition of MathWorld and CLRCP to the combination of references does not remedy their deficiencies.

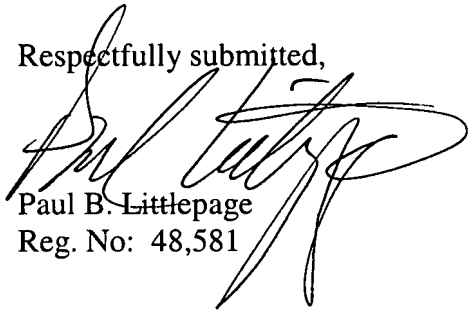
Thus, because the cited combination of references does not supply all elements of the current claims, *prima facie* obviousness does not exist and Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. In the event that substantive matters are felt to remain, the Examiner is invited to telephone the undersigned at (510) 769-3507.

Quine Intellectual Property Law Group, P.C.
P.O. BOX 458
Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877

Respectfully submitted,



Paul B. ~~Littl~~epage
Reg. No: 48,581